REMARKS

Claims 18, 21, 23 and 25-30 are pending in the instant application. Applicant respectfully request consideration of the Claims in light of the remarks presented below.

Claim Amendments

Claims 18, 25 and 28 have been amended. Support for amended Claims 18 and 25 is found in the specification at page 8-9, lines 15-10. Support for amended Claim 28 is found in the specification at page 6, lines 4-9. No new matter is added by the amendment of Claims 18, 25 and 28. Accordingly, entry into the instant Application is proper and respectfully requested

Nonstatutory Double Patenting

Claims 18, 25 and 28 stand rejected under the judicially created doctrine of obviousness-type double-patenting as being unpatentable over claims 1-19 of U.S. Patent No. 5,734,021 in view of *Duprat* and *Yatani* as evidenced by *Krapivinsky*. Applicant notes that U.S. Patent No. 5,734,021 contains claims 1-5 and not claims 1-19 as stated in the Office Action of October 7, 2004, therefore Applicant will assume that the rejection is directed to claims 1-5 of U.S. Patent No. 5,734,021. Applicant respectfully traverse the double-patenting rejection.

The standard for an obviousness-type double patenting rejection is the same as for a rejection under 35 U.S.C. § 103 (*see* MPEP § 804), except that only the claims and not the underlying disclosure of the issued patent may be considered as prior art. Therefore, for this rejection to be proper, the claims of the '021 patent and cited references must 1) disclose each element of the presently claimed invention; 2) provide motivation to combine and modify these teachings to obtain the present invention; and 3) provide a reasonable expectation of success in obtaining the present invention. These criteria are not met in the present rejection.

Claims 1-5 of U.S. Patent No. 5,734,021 are directed to compositions comprising a naturally occurring or non-naturally occurring potassium KGA (Kir) channel protein. In contrast, the pending claims of the present application are directed to methods of screening for agents that inhibit the activity of a Kir3.0 channel that contain at least two different Kir channel

proteins. Based on these differences the screening methods using a Kir channel protein are not obvious over claims to a naturally occurring and non-naturally occurring Kir protein. Furthermore, claims 1-5 of U.S. Patent No. 5,734,021 in view of *Duprat* and *Yatani* as evidenced by *Krapivinsky* (as discussed in more detail below) do not teach or suggest a method for screening for agents that inhibit the activity of a Kir3.0 channel.

Additionally, the Examiner asserts that the potassium KGA channel of U.S. Patent No. 5,734,021 has 100% amino acid identity with *claimed* SEQ ID NO: 2 and 57% identity with *claimed* SEQ ID. NO: 6. The regions of high nucleic acid sequence identity will inherently hybridize under stringent conditions. Office action of October 7, 2004, page 3 (emphasis added). Applicant asserts that the rejection of Claims 18, 25, and 28 is improper, because Claims 18, 25 and 28 do not *claim* SEQ ID NO: 2, nor do they *claim* SEQ ID NO: 6 as the Examiner asserts.

Applicant respectfully requests withdrawal of the double-patenting rejection.

Claim Rejections - 35 U.S.C. §112, First Paragraph

Claims 18-24 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not being described in the specification so as to convey that Applicant has possession of the claimed invention. Applicant respectfully brings to the Examiners attention that Claims 19, 20, 22, and 24 were previously canceled. *See* Amendment and Response, filed May 24, 2004. Assuming that the current rejection is directed to pending Claims 18, 21 and 23, the rejection is traversed.

Applicant respectfully reminds the Examiner that he previously suggested that the pending claims be amended to recite a specific sequence. See Statement of the Substance of Interview, filed May 24, 2004. Specifically, the Examiner suggested the claims be amended to recite polypeptides 50% identical to the specific Kir polypeptides that are structurally identified by amino acid sequence. *Id.* In reliance on the Examiner's suggestion, and in order to facilitate prosecution, Applicant amended Claims 18, 21 and 23 to recite polypeptides 50% identical to the specific Kir polypeptides that are structurally identified by amino acid sequence. *See* Amendment and Response, filed May 24, 2004.

Applicant respectfully submits that the current rejection of Claims 18, 21 and 23 under §112, first paragraph is inconsistent with the April 29, 2004 Interview in which the Examiner suggested the pending claims be amended to recite polypeptides 50% identical to the specific Kir polypeptides and request that the Examiner remove the rejection.

In addition, Applicant again asserts that the structure and function of Kir3.0 (*e.g.*, comprised of individual members Kir3.1, Kir3.2, Kir3.3, and Kir3.4) is adequately identified and described in the claims, as well as in the specification. The specification as filed, sets forth specific examples of nucleic acids encoding the Kir3.1, Kir3.2, Kir3.3 and Kir3.4 polypeptides. The amendment of the claims to recite homology to the polypeptides produced from the recited nucleic acid sequences provides a structural definition of Kir3.0 polypeptides.

Furthermore, the unique properties of the functional multimeric Kir3.0 channels are demonstrated (page 27, lines 7-9; 24-25) in *Xenopus laevis* oocytes which are injected with atrial mRNAs (and mRNAs encoding serotonin receptor) wherein multimeric Kir3.0 channels are formed and inward rectifiers are opened by serotonin that is mediated by G-protein (*e.g.*, $G\beta_1\gamma_2$) activation. These multimeric Kir3.0 channels are further expressly demonstrated to exhibit the unique properties of conducting inward but not outward K^+ current, of exhibiting blockage by low concentrations of Ba^{2+}, and of exhibiting channel conductance that is dependent on voltage as well as $(E-E_K)$ (page 27, lines 8-12).

The specification further demonstrates that coexpression of Kir3.2/Kir3.1 in *Xenopus laevis* oocytes produces large G-protein mediated inward currents relative to the individual expression of either Kir3.2 or Kir3.1 (page 31, lines 2-9). The specification additionally describes that coexpression of Kir3.3/Kir3.1 in *Xenopus laevis* oocytes produces large inward currents relative to the expression of Kir3.3 alone (page 33, lines 14-24). Moreover, coexpression of Kir3.3 and Kir3.2 in *Xenopus laevis* oocytes produces small inward currents relative to the expression of Kir3.2 alone (page 33, lines 25-28).

For the foregoing reasons, the function and structure of the functional Kir3.0 (*e.g.*, Kir3.1, Kir3.2, Kir3.3, Kir3.4) heteromultimeric channels recited in Applicant's claims are more than sufficiently described in the specification in such a way as to reasonably convey to one skilled in the art that the Applicant had possession of the claimed invention at the time the

application was filed. Applicant respectfully asserts that Claims 18, 21 and 23 are in compliance with 35 U.S.C. §112, first paragraph, and request withdrawal of the rejection.

Rejection Under 35 U.S.C. § 102(b) - *Yatani, et al.* with evidence from *Krapivinsky, et al.*

Claims 18, 25 and 28 stand rejected are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by *Yatani* with evidence from *Krapivinsky*. The rejection as it stands against amended Claims 18, 25 and 28 is respectfully traversed.

The Examiner has previously asserted that *Yatani* teaches a method of reducing the current of a Kir3.0 channel with NAD and PTX. Office Action of February 11, 2002, pages 8-9. The Examiner currently asserts the isolated cells of *Yatani* are provided with heteromeric subunits to form inward rectifier channels prior to the patch clamp. Further, the Examiner asserts the *Yatani* channels as the same channels disclosed by *Krapinvinsky. See* Office action of October 7, 2004, page 4.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Furthermore, "[t]o serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." Continental Can Co. USA v. Monsanto Co., 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

Amended Claim 18 recites a method for screening for agents which inhibit the activity of a Kir3.0 channel comprising combining at least two different inward rectifier, G-protein activated, mammalian, potassium Kir3.0 polypeptides in a cell to form a functional Kir3.0 channel, combining the candidate agent with the Kir3.0 channel under conditions which permit inward K+ current, and determining the induced current, wherein a reduction in the induced current in the presence of the candidate agent as compared to a control is

indicative that the agent inhibits the activity of a Kir3.0 channel. The Kir3.0 polypeptides are selected from the group consisting of Kir3.0 polypeptides having at least about 50% amino acid sequence identity with a Kir3.1 polypeptide encoded by the nucleic acid of SEQ ID NO: 7, a Kir3.2 polypeptide encoded by the nucleic acid of SEQ ID NO:11, a Kir3.3 polypeptide encoded by the nucleic acid of SEQ ID NO:12 and a Kir3.4 polypeptide encoded by the nucleic acid of SEQ ID NO:16. Thus, amended Claim 18 requires a cell and at least 50% identity to Kir3.0 polypeptides encoded by the recited nucleic acid sequences.

Claim 25 recites a method for screening for agents that inhibit the activity of a Kir3.0 channel, the method comprising combining at least two different inward rectifier, G-protein activated, mammalian, potassium Kir3.0 polypeptides in a cell to form a functional Kir3.0 channel, combining the candidate agent with said Kir3.0 channel under conditions that permit inward K+ current, determining the induced current, wherein a reduction in said induced current in the presence of said agent as compared to a control is indicative that said agent inhibits the activity of a Kir3.0 channel. The Kir3.0 polypeptides are selected from the group consisting of polypeptides encoded by nucleic acids that hybridize under low stringency conditions with a complement of the nucleic acid of SEQ ID NO: 7, SEQ ID NO:11, SEQ ID NO:12, or SEQ ID NO:16.

Claim 28 is dependent on Claim 18.

Applicant respectfully asserts that *Yatani* does not teach the invention as defined in amended Claims 18, 25 and 28. The analysis of the potassium channels of *Yatani* is performed using inside-out patches of membranes; thus *Yatani* does not disclose the use of cells that combine heteromeric Kir3.0 subunits or cells that synthesize multimeric Kir3.0 channels. Furthermore, *Yatani* does not identify the composition of the channels studied and no sequence information is disclosed. Moreover, *Yatani* does not describe a screening method to identify agents that modulate K^+ currents of the Kir channels. As such, *Yatani* cannot anticipate Claim 18, 25 and 28 which recite homology to Kir3.0 encoded by specific nucleic acid sequences.

Krapivinsky cannot be used supplement *Yatani* in such a way as to show that *Yatani* anticipates Claims 18, 25 and 28. *Krapivinsky* was cited by the Examiner as showing that

the channels of *Yatani* are heteromultimers. However, *Krapivinsky* does not show that the channels of *Yatani* necessarily are composed of Kir3.0 polypeptides that are selected from the group consisting of Kir3.0 polypeptides having at least about 50% amino acid sequence identity with a Kir3.1 polypeptide encoded by the nucleic acid of SEQ ID NO: 7, a Kir3.2 polypeptide encoded by the nucleic acid of SEQ ID NO:11, a Kir3.3 polypeptide encoded by the nucleic acid of SEQ ID NO:12, and a Kir3.4 polypeptide encoded by the nucleic acid of SEQ ID NO:16.

Likewise, *Krapivinsky* does not show that that the channels of *Yatani* necessarily are composed of Kir3.0 polypeptides selected from the group consisting of polypeptides encoded by nucleic acids that hybridize under low stringency conditions with a complement of the nucleic acid of SEQ ID NO: 7, SEQ ID NO:11, SEQ ID NO:12, or SEQ ID NO:16 as required by Claim 25.

Applicant respectfully requests that the 35 U.S.C. § 102(b) rejection of amended Claims 18 25 over *Yatani, et al.* with evidence from *Krapivinsky, et al.* be withdrawn. Claim 28 ultimately depend from Claim 18 and is therefore likewise not anticipated.

Rejection Under 35 U.S.C. § 102(b) - *Karschin et al.* with evidence by *Krapivinsky et al.*

Claims 18, 25 and 28 stand rejected under 35 U.S.C. § 102(b) as being anticipated by *Karschin* with evidence from *Krapivinsky.* The rejection against amended Claims 18, 25 and 28 is respectfully traversed.

The Examiner asserts that *Karschin* discloses the 5-HT/5-HT receptor and Ach/Ach receptor activations of I(Kach) inwardly rectifying potassium current. Office action of October 7, 2004, page 5. The Examiner further states that the isolated cells of *Karschin* continuously synthesizes and combine the heteromeric subunits to form the inward rectifer channels meeting the amended claim limitation. The Examiner relies on *Krapinvinsky* to teach that the *Karschin* potassium channels are inherently heteromultimers.

The Applicant respectfully asserts that *Karschin* does not teach the invention as defined in amended Claim 18, 25 and 28. *Karschin* discloses heterologously expressed

serotonin receptors which are *activated* by serotonin and acetylcholine in primary cultures of atrial (cardiac) myocytes. These arguably contain endogenous K^+ channels, but the activated channel is not conclusively a Kir channel. More importantly, nothing in *Karschin* teaches or discloses a method for screening for agents that inhibit the activity of a Kir3.0 channel.

Furthermore, although *Karschin* may disclose that recombinantly expressed serotonin receptors couple to native K^+ channels (*e.g.,* via a G-protein interaction) that are endogenous to rat atrial myocytes, nothing in the reference teaches or discloses combining at least two different inward rectifier, G-protein activated mammalian, potassium Kir3.0 polypeptides in a cell to form functional Kir3.0 channels.

As with the *Yatani* reference, *Krapivinsky* cannot be used to supplement *Karschin* in such a way as to show that *Karschin* anticipates Claim 18, 25 and 28. *Krapivinsky* was cited by the Examiner as showing that the channels of *Karschin* are heteromultimers. However, *Krapivinsky* does not show that that the channels of *Karschin* necessarily are composed of Kir3.0 polypeptides.

Applicant respectfully requests that the 35 U.S.C. § 102(b) rejection of amended Claim 18, 25 and 28, over *Karschin* with evidence from *Krapivinsky* be withdrawn.

Rejection Under 35 U.S.C. § 102(a) - Duprat, *et al.*

Claims 18, 20, 23 and 25-30 stand rejected under 35 U.S.C. § 102(b) as being anticipated by *Duprat.* Because Claim 20 has been previously canceled and Claim 21 has previously been rejected under 35 U.S.C. § 102(b) as being anticipated by *Duprat,* Applicant assumes that the current rejection applies to Claim 21 and not canceled Claim 20. See Amendment and Response of May 24, 2004. The rejection to Claims 18, 21, 23 and 25-30 is respectfully traversed.

The Examiner asserts that *Duprat* discloses different Kir 3.0 channel subfamily members expressed in cells and relies on reasons for the rejection set for in previous Office Actions. The Examiner previously argued, that since the Mg^{2+} and ATP blocks or inhibits

the potassium current, it is an inhibitor compared to the control without Mg^{2+}. Office Action of February 11, 2002, at page 10. Further, the Examiner argues that Figure 2 of *Duprat* discloses a voltage-current graph which shows that while the inward rectification is abolished the current is greater without magnesium than with magnesium thus showing inhibition or decrease or reduction in current. Office Action of May 20, 2003, at page 6.

Pending independent Claims 18, 21, 25 and 26 require the element of combining the candidate agent with a Kir3.0 channel under conditions that permit inward K+ current. *Duprat* neither discloses nor suggests the method of combining the candidate agent with a Kir3.0 channel under conditions that permit inward K+ current as required by the pending claims. Applicant points out that ATP and Mg^{2+} factors are necessary for the activity of the channels disclosed in *Duprat et al.* Removal of either ATP or Mg^{2+} from the channels results in a decrease in channel activity (page 660-661) while inclusion of these factors restores channel activity (pages 660- 661). Importantly, Figure 2 shows that "K^+ currents generated by GIRK1, GIRK2, and GIRK4 exhibit a strong inward rectification which is abolished in Mg^{2+} free internal solution. ... The strong Mg^{2+} -dependent inward rectification is maintained for currents produced by the heteromeric channels. *Duprat et al.* at *660-661.* In fact, *Duprat* discloses that ATP and Mg^{2+} are required for inward rectification. See *Duprat et al.* Abstract and page 660.

In addition, the pending claims require the element of "combining the candidate agent with said Kir 3.0 channel" (Claim 18, 25, 28), or "combining a candidate agent with a functional Kir3.0 channel" (Claim 21, 26, 28), or "contacting the Kir3.0 channel with one or more candidate-inhibiting material" (Claims 23, 27, 30). *Duprat* neither discloses nor suggests the method of combining or contacting the agent with a Kir3.0 channel as required by the pending claims. As such, *Duprat* fails to teach the element of combining or contacting the agent with a Kir3.0 channel as required by the pending claims. Accordingly, *Duprat*, fails to anticipate Claims 18, 21, 23 and 25-30.

As distinguished from *Duprat*, Applicant's Claims 18, 21, 23 and 25-30 require a functional Kir3.0 channels, rather than channels without components which are associated with channel activity (*see* abstract, lines 10-12 and page 661, lines 662, lines 1-2; page 660, line 15

and page 661, lines 1-2). Moreover, Applicant's claims require combining (Claim 18, 21, 25, 26, 28 and 29) or contacting (Claim 23, 27 and 30) Kir3.0 channels with candidate inhibitory agents or channel-inhibiting materials in which the presence of the inhibiting agent or material causes a reduction, decrease, or inhibition of the Kir3.0 channel activity. *Duprat* in contrast, discloses the absence, rather than the presence of ATP or Mg^{2+} for reducing, inhibiting or decreasing the activity of the channel. In summary, as distinguished from the channels disclosed in *Duprat*, Applicant's channels are functional (*e.g.*, permit inward K^+ current) in the absence of a candidate agent and, moreover, require the inclusion of a candidate agent or channel-inhibiting material for reduction or inhibition of inward K^+ current.

Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 102(a) rejection of Claims 18, 21, 23 and 25-30.

Conclusion

On the basis of the amendments and remarks presented herein, Applicant submits that the claims are in form for allowance and early notice of such is requested. If the Examiner believes that there are remaining issues which may be resolved by telephone, he is invited to call the undersigned at (415) 781-1989.

Respectfully submitted,

DORSEY & WHITNEY LLP

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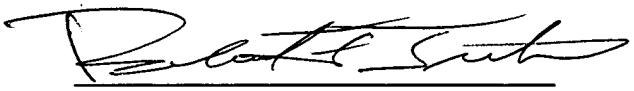

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